ECHA response to HEAL's report "How the EU risks greenlighting a pesticide linked to cancer"

Executive summary

Opinion on Glyphosate

The European Chemicals Agency's Committee for Risk Assessment (RAC) recently (30 May 2022) adopted its opinion to retain the current harmonised classification for glyphosate as a substance which causes serious eye damage and is toxic to aquatic life. Based on a wide-ranging review of the scientific evidence, the Committee also concluded that no classification for carcinogenicity, mutagenicity or toxicity to reproduction is warranted for glyphosate.

The opinion[1] considers all of the information in the extensive harmonised Classification and Labelling (CLH) report[2] as prepared by the Assessment Group for Glyphosate (AGG)[3] as well as all comments received during the consultation on the proposal which was published on the ECHA website in September 2021.

The 2016 (Germany) and 2021 (France, Hungary, The Netherlands and Sweden) evaluations of the harmonised classification and labelling of glyphosate independently reviewed the available data. The latter review considered many more studies from the public literature than the earlier one.

HEAL claims as regards tumour incidences

In June 2022, the Health and Environment Alliance (HEAL) published a report (hereafter referred to as the HEAL report) in which it is argued that "*the cancer studies provided by pesticide companies for the carcinogenicity assessment of glyphosate show the clear potential for the substance to cause cancer*".

The main claim in the HEAL report is that tumours in 10 out of 11 carcinogenicity studies were dismissed from the assessment. However, this allegation is unfounded - **the tumours in the carcinogenicity studies were not dismissed from the assessment**, as incorrectly claimed in the HEAL report. These tumour incidences (as well as other findings not mentioned in the HEAL report) observed in the carcinogenicity studies were in fact central to the assessment and hence they were analysed in detail by France, Hungary, The Netherlands and Sweden in preparing the classification proposal as well as by RAC in evaluating it.

More specifically, France, Hungary, The Netherlands and Sweden and RAC evaluated in detail the tumour types observed in 7 studies in rats and in 5 studies in mice. In doing so, they considered the strength of the statistical evidence, dose-response relationships, concurrent and historical control data and the biological relevance of the findings.

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[1] The RAC opinion, CLH report and responses to comments received during the consultations on glyphosate can be accessed from https://iuclid6.echa.europa.eu/en/web/guest/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e185e41a77

[2] This was a combined CLH report (CLH process) and draft Renewal Assessment Report (dRAR volume 1 – EFSA process) but is referred to throughout this document only as the CLH report.

[3] Comprising France, Hungary, The Netherlands and Sweden – for more information: https://ec.europa.eu/food/plants/pesticides/approval-active-substances/renewal-approval/glyphosate/assessment-group_en

It should be noted that these are the same 12 animal studies considered for carcinogenicity by Germany as the submitter of the classification proposal in 2016 and evaluated by RAC in 2017, with the same outcome. RAC also took on board all of the comments received during the consultation of the CLH report prepared by France, Hungary, The Netherlands and Sweden from HEAL and Prof. Portier and they together with Dr. Clausing were given a possibility to participate in the meetings of RAC (in the key issues discussion in March, 2022, in the RAC CLH Working Group meeting in April 2022 as well as at the plenary meeting in May 2022) to express their views.

In addition to these animal studies, many epidemiology studies (which provided information from human exposure to glyphosate) were also considered in the CLH report as well as in the deliberations of RAC. Currently, the key epidemiology study[4] does not show concern for carcinogenicity arising from exposure to glyphosate.

Transparency and Independence

RAC currently has 45 members nominated by the EU/EEA Member State Competent Authorities but appointed by the Management Board of ECHA in their personal capacity as scientists. The Member States guarantee at least 50% of the time of their nominees to RAC. The eligibility criteria for membership of RAC are strict. The membership is screened for conflict of interest on an annual basis and members are requested to declare any other potential conflicts to each agenda of the Committee. The CV's and declarations of interest are published on the ECHA website[5].

Competence of RAC and the competent authorities of France Hungary, The Netherlands and Sweden

France, Hungary, The Netherlands and Sweden came to its conclusion following an independent assessment of the data by the many Member State experts involved, and subsequently these data and conclusions were analysed by the independent experts of RAC. Members of RAC are experts in toxicology and more critically, experts on application of the CLP criteria to toxicological and epidemiological findings. The work was led by the appointed Rapporteurs[6] and their support teams of advisors, who drafted the opinion of the Committee for RAC's consideration. In accordance with its mandate, RAC weighed all the evidence in arriving at its conclusions on the classification of glyphosate, including no classification for carcinogenicity. RAC's detailed assessment is provided in the adopted opinion[1].

[4] The Agricultural Health Study, a prospective cohort of licensed pesticide applicators from North Carolina and Iowa (USA) (Andreotti *et al*. Glyphosate use and cancer incidence in the Agricultural Health Study. J Natl Cancer Inst (2018) 110(5): doi: 10.1093/jnci/djx233)

[5] https://echa.europa.eu/about-us/who-we-are/committee-for-risk-assessment#:~:text=Committee%20for%20Risk%20Assessment%20The%20Committee%20for%20Risk,final%20decisions%20are%20taken%20by%20the%20European%20Commission.

[6] For further information see 9fc28e72-0142-6d36-1438-7512f3e17fc6 (europa.eu)

ECHAs considered response to specific issues raised in the HEAL Report

The roles of different parties in the process

In the harmonised classification and labelling (CLH) process the task of the ECHA Committee for Risk Assessment (RAC) is to adopt an opinion on whether a substance should or should not be classified in one or more hazard classes or their categories. To date RAC has adopted opinions on over 500 CLH dossiers, at the rate of ca. 50 per year, many concerning carcinogens, mutagens and reproductive toxicants.

The opinion of RAC is primarily based on the information contained in the CLH report which is prepared by a dossier submitter (DS, in this case France, Hungary, The Netherlands and Sweden) as well as the information received during the public consultation of the CLH report. RAC does this objectively, focusing exclusively on the hazardous intrinsic properties of the substance based on the available data, using a WoE approach assessing positive and negative findings as required by the CLP Regulation. This does not take conditions of use or risk into account, or any downstream consequences of classification in other legislation. Further details on the process is available on the ECHA website at Harmonised classification and labelling (CLH) - ECHA (europa.eu).

The definitions of what constitutes sufficient evidence to classify a substance as a carcinogen by the International Agency for Research into Cancer (IARC) and under the CLP Regulation are similar and this is sometimes taken as a sign that outcomes of the respective evaluations of substances for carcinogenicity must be identical. However, the evidence base for the classification proposal by the dosser submitter under CLP is wider. The CLP Regulation requires that all the "relevant available information" be examined, including industry studies, rather than exclusively that which is in the public domain, as is the case for IARC. Accordingly, the evidence to be weighed differs.

Assessment of the data

The CLH report submitted by France, Hungary, The Netherlands and Sweden addressed all the hazard classes in the CLP Regulation which are applicable to an active substance used in plant protection products.

The HEAL report has focussed on the assessment conducted by France, Hungary, The Netherlands and Sweden leading to a conclusion for no classification for carcinogenicity. The main part of any carcinogenicity study which is conducted in accordance with standard (OECD) test guidelines uses approximately 400 rats or mice, the survivors of whom after 18 months to 2 years have lived a substantial proportion of their life-expectancy at the end of the in-life phase of the study. Therefore, even without any exposure to substances which may be carcinogenic, it is inevitable that a substantial number of animals will have developed tumours of various types. The focus of the subsequent analyses of the data by regulatory bodies such as RAC is whether the tumours are likely to be the result of exposure to the substance. Furthermore, strains of laboratory rats and mice are known to be susceptible to certain stimuli, including their tendency to spontaneously develop certain types of tumour. Therefore, tumours are first and foremost compared to the background incidence in the control groups of animals not exposed to the substance under investigation.

For most active substances used in plant protection products, there are one or two such carcinogenicity studies available. In the case of glyphosate, which is among the active substances which has been most extensively studied for its carcinogenicity, the data relating to tumours seen in 7 studies conducted using rats and 5 studies conducted in mice have been analysed to establish whether there is a relationship to tumour development arising from exposure to the substance. The standard methods employed for these

analyses to determine the biological significance of the findings include statistical analyses, establishing whether there are dose-response relationships to tumour formation and how the tumour findings compare with the concurrent and historical control. In addition, according to the CLP Regulation there is an obligation to weigh all the available evidence in coming to a conclusion on classification[7]. The extent to which the findings are consistently observed between studies also needs to be considered, because with comparable doses, it would be expected that adverse effects would be reproducible in other comparable studies. Consistency of the findings between studies is also considered.

France, Hungary, The Netherlands and Sweden conducted an extensive evaluation of the ten tumour types seen in these studies. No tumour types were dismissed, but they were all assessed against the criteria for classification in the CLP Regulation.

Statistical analyses

Details of the assessments of France, Hungary, The Netherlands and Sweden and RAC are provided in the CLH report and RAC opinion[1], respectively. Some of the statistical analyses are dependent on which test is used. None of the tumours referred to in the HEAL report were statistically significant using pairwise comparison with two-sided testing, but some were statistically significant following two-sided testing using the trend test. Additional findings were also statistically significant when one-sided pairwise comparisons or trend tests were employed. Further information on statistical testing referred to in this document can be found in OECD GD 116[8] and the references therein.

Extensive statistical analyses have been conducted on the data from the large number of studies addressing the carcinogenicity of glyphosate. In its report, HEAL has argued that unjustified statistical methods have been used.

Statistical analyses used were considered and a reanalysis conducted in the harmonised classification and labelling (CLH) dossier submitted in 2016 by the (then) dossier submitter Germany. The analyses were considered appropriate in the RAC opinion in 2017.

As acknowledged by the authors of the HEAL report, France, Hungary, The Netherlands and Sweden has included the results both from a trend test and a pairwise comparison for each of the tumour findings in the studies analysed. The main statistical methods used in the animal studies were the Fisher's exact test[8] for pairwise comparisons and the Cochran-Armitage trend test[8]. In their detailed assessment of findings, France, Hungary, The Netherlands and Sweden repeated both the pairwise and trend test statistical calculations for the findings from relevant studies. In addition, for one study in mice (CA 5.5/016, 2001), a Peto-analysis[8] was performed for the induction of malignant lymphomas. Statistical significance is one part of the evaluation and has been included in the

[7] CLP Regulation, Annex I, 1.1.1.3 (also quoted in Art 9(3) of CLP): "*A weight of evidence determination means that all available information bearing on the determination of hazard is considered together, such as the results of suitable in vitro tests, relevant animal data, information from the application of the category approach (grouping, read-across), (Q)SAR results, human experience such as occupational data and data from accident databases, epidemiological and clinical studies and well-documented case reports and observations. The quality and consistency of the data shall be given appropriate weight. Information on substances or mixtures related to the substance or mixture being classified shall be considered as appropriate, as well as site of action and mechanism or mode of action study results. Both positive and negative results shall be assembled together in a single weight of evidence determination*" (emphasis added).

[8] OECD Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Test Guidelines 451, 452 And 453, 2nd Edition, 2012 (https://doi.org/10.1787/9789264221475-en), referred to as OECD GD 116 throughout this document

assessment, but the presence of statistically significant results does not automatically lead to classification.

According to OECD GD 116 (point 384, p 133), reproduced here in full "*In a carcinogenicity study, the expectation is often that the change will be an increase in tumours in the treated group so a one-sided test may be considered more appropriate, although this can be controversial. If the treatment could also be protective (i.e., reduce tumour incidence or delay it) then a two-sided comparison may be more appropriate. Regulatory authorities may have specific opinions. For instance, the US EPA (2005) notes that either "a two-tailed test or a one-tailed test may be used*" (emphasis added). Therefore, in accordance with GD 116 it is also acceptable to conduct either one or two tailed tests.

France, Hungary, The Netherlands and Sweden included in the CLH report the results for both one- and two-sided testing from trend as well as pairwise comparison and of particular note is that the data from the Portier (2020) paper for the one-sided testing from both types of tests was included alongside the 2-sided data in the tables describing each tumour type.

The HEAL report states that the information from two-sided testing was used "*without explaining its choice*". However, contrary to this assertion, the choice has been explained by France, Hungary, The Netherlands and Sweden (on page 257 of the CLH report). It was first noted that "*OECD Guidance Document 116 stipulates "The choice of whether to use a one- or two-sided test should be made at the design rather than the analysis stage""* and then (after quoting the rest of the paragraph) that "*in the AGG overall analysis on the tumour relevance, two-sided testing was applied as this is in line with how the statistical analysis was established in the study protocols of the available carcinogenicity studies*."

Furthermore, from the comments received during the consultation on the CLH report submitted by France, Hungary, The Netherlands and Sweden, it is clear that not all statisticians agree with the assertion made in the HEAL report that "*since glyphosate is not a protective treatment against cancer, the use of the two-sided statistical test is incomprehensible*", because one party (in Comment 21) noted that they had concerns about the use of one-sided significance levels (exclusively in the direction of a positive association) to summarise the results of the glyphosate rodent studies and that "*the use of one-sided p-values for positive associations will not only increase statistical power, but will also increase the number of false positive findings*". The comment also pointed to the findings of Crump *et al* (2020[9]), in which it is stated, after analysing ten of the rodent carcinogenicity studies for positive and negative dose-response trends using the same statistical trend test, that they "*found more evidence for negative dose-response trends than positive"* i.e., as expressed in the comment "*more tumor types showing significant decreases in tumor rates with increasing glyphosate levels than there were showing significant increases*". The focus of the analyses of France, Hungary, The Netherlands and Sweden as well as RAC was on the findings indicating increased tumours, and these were analysed in detail.

Dose response relationships

In the HEAL report, on page 19 findings in four studies are highlighted. The bar graphs used suggest that the dose-response relationships are more steep or more linear than when the findings are graphed to scale on both axes. Details of the assessments of France,

[9] It was disclosed in the paper that some of the authors were on the EPA Federal Insecticide, Fungicide, and Rodenticide Act Science Advisory Panel (SAP), which met to review an EPA document on glyphosate on December 13–16, 2016. One of the authors testified before this panel on behalf of Monsanto and had a 1-year consulting agreement with Monsanto

Hungary, The Netherlands and Sweden and RAC are provided in the CLH report and RAC opinion, respectively.

The skin keratoacanthoma findings in study R-6 (1990) were not statistically significant by either pairwise comparison or by trend test (two-sided testing). RAC noted that skin keratoacanthoma is a benign tumour which is shown to be rather common in aged male rats and in fact were only reported in male rats (and not in female rats and male and female mice). Furthermore, no malignant squamous cell carcinomas were reported. In humans, this type of benign skin tumour is associated with multiple exposure to sunlight, whereas in rats, which are most likely only exposed to artificial light, the cause of skin keratoacanthomas is unknown. RAC concluded that the increase in skin keratoacanthomas only reported in male rats is not of sufficient relevance for classification for carcinogenicity. A more detailed analysis of the skin keratoacanthoma findings from this and other studies where this was observed is in the RAC opinion (under the heading "*Skin tumours"*).

The statistical significance of malignant lymphomas observed in studies M2 (2001) and M1 (2009) were noted by France, Hungary, The Netherlands and Sweden to be very much dependent on the statistical method used for analysing the data. In the 2009 study, the findings were statistically significant when the trend test was applied (either one- and two-sided), but not when a pairwise comparison was performed (but were statistically significant with a one-sided pairwise test (Portier, 2020)). The increased incidence in the 2001 study was not confirmed either by the trend test (one- and two-sided) or by a two-sided pairwise test but only when using a one-sided pairwise test and one-sided Peto-analysis. As is clear from Figure 1 of the HEAL report, the increased incidence in study M2 (2001) was against a high background incidence. RAC has reviewed all of the data and in a weight of evidence assessment concludes that the reported incidences of malignant lymphoma in CD-mice and Swiss mice is not considered related to glyphosate exposure. A more detailed analysis of the malignant lymphoma findings from these and other studies where this tumour type was observed is in the RAC opinion (under the heading "*Malignant lymphoma*").

Regarding the kidney tumours observed in study M5, 1983, these were only seen in males, when a very high top dose was used (4841 mg/kg bw/day) and no increase was reported in related preneoplastic lesions. The histopathology findings were reanalysed at the request of the EPA (1986)[10]. The Pathology Working Group noted that differentiation between tubular cell adenoma and tubular cell carcinoma is not always clearly apparent and both lesions are derived from the same cell type. Accordingly, the combined incidences were used in the statistical analysis by France, Hungary, The Netherlands and Sweden as well as by RAC. A more detailed analysis of the kidney tumour findings from this and other studies where this was observed is in the RAC opinion (under the heading "*Renal neoplasms")*.

Use of Historical control data (HCD)

The HCD data is only one of the considerations in assessing the biological significance of each tumour type. The RAC opinion is very transparent in the use of the HCD and they are used according to the description of the use of HCD data in the CLP Guidance[11] (i.e. ideally

[10] Report accessible from https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_11-Mar-86_211.pdf)

[11] Concerning the use of HCD, CLP Guidance (ECHA, 2017) states that "*Use of historical control data should be on a case by case basis with due consideration of the appropriateness and relevance of the historical control data for the study under evaluation. In a general sense, the historical control data set should be matched as closely as possible to the study being evaluated. The historical data must be from the same animal strain/species, and ideally, be from the same laboratory to minimise any potential confounding due to variations in laboratory conditions, study conditions, animal suppliers, husbandry etc. It is also known that tumour incidences in control*

from the same performing laboratory and within a period of up to around 5 years of the study). Furthermore, the HCD data is only one of the considerations in assessing the biological significance of each tumour type. The HCD are included and discussed in the RAC opinion for glyphosate in the same way as has been done in other RAC opinions.

RAC fully agrees with the OECD GD 116 statement that "*the concurrent control group is the most important consideration in the testing for increased tumour rates*". In relation to the 1997 study in mice which is specifically referred to in the HEAL report, France, Hungary, The Netherlands and Sweden did indicate that the range was 3.8% to 19.2% with a mean of 7% (giving an indication of the spread of the HCD values). In addition, in the RAC opinion it is noted that "*six of the seven studies had a control incidence ≤ 6% leading to a range of 3.8% to 6% with a mean of 4.92%. Therefore, when taking into account HCD from the six studies the incidences of malignant lymphoma in male mice exceeded the HCD*". However, in this specific study, the increases in tumour incidences were only observed at a very high dose (4348 mg/kg bw/day).

The limit dose

The HEAL report asserts that France, Hungary, The Netherlands and Sweden dismissed all the observed increases in two types of tumours in mice since these exceeded the limit dose. In the CLH report it is noted that the OECD TG 453 states that "*a limit of 1000 mg/kg bw/day may apply except when human exposure indicates the need for a higher dose level to be used*". Furthermore, in OECD GD 116, it is stated that "*As indicated in the Test Guidelines, a top dose not exceeding 1000 mg/kg body weight/day may apply except when human exposure indicates the need for a higher dose level to be used*". Thus, setting a maximum dose of 1000 mg/kg bw/day for glyphosate is considered appropriate as the exposure to humans is far below this level. The findings at doses greater than 1000 mg/kg bw/day were not dismissed, but were considered in this context.

At some of the high doses used the relevance of findings seen in long-term studies to humans may be questionable. Doses above 1000 mg/kg bw/day are high doses when used over 18 months or 2 years and the possibility that there are then other factors coming into play increases. This applies even more so to those in excess of 4000 mg/kg bw/d. This needs to be (and has been) taken into account in the weight of evidence assessment.

Weighing all the data

In the CLH report, France, Hungary, The Netherlands and Sweden considered each study individually as well as each of the specific tumour types observed across the studies.

In the HEAL report it is argued that there is an indisputable basis for a Category 1B classification for carcinogenicity. In support HEAL quotes Annex 1, 3.6 of the CLP Regulation, specifically the provision relating to what constitutes "*sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols*".

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animals can change over time, due to factors such as genetic drift, changes in diagnostic criteria for pathological changes/tumour types, and husbandry factors (including the standard diet used), so the historical data should be contemporary to the study being evaluated (e.g. within a period of up to around 5 years of the study). Historical data older than this should be used with caution and acknowledgement of its lower relevance and reliability".

This argumentation ignores the obligation from the CLP Regulation to weigh all of the available evidence in each case. In Recital 33, of the CLP Regulation, this is reflected as follows: "*Recognising that the application of the criteria for the different hazard classes to information is not always straightforward and simple, manufacturers, importers and downstream users should apply weight of evidence determinations involving expert judgement to arrive at adequate results*."

In Art 9(3) of the CLP Regulation and in Annex I (Section 1.1.1 titled "*The role and application of expert judgement and weight of evidence determination*") the following provisions are set:

- Article 9(3): "*Where the criteria cannot be applied directly to available identified information manufacturers, importers and downstream users shall carry out an evaluation by applying a weight of evidence determination using expert judgement in accordance with section 1.1.1 of Annex I to this Regulation, weighing all available information having a bearing on the determination of the hazards of the substance or the mixture, and in accordance with section 1.2 of Annex XI to Regulation (EC) No 1907/2006*" (emphasis added).

- Section 1.2 of Annex XI to the REACH Regulation (referred to in Art 9(3) of the CLP Regulation, quoted above) it states that "*There may be sufficient weight of evidence from several independent sources of information leading to the assumption/ conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion*".

- Annex I (section 1.1.1.3, quoted earlier[3]) (also referred to in Art 9(3), quoted above) states that "*A weight of evidence determination means that all available information bearing on the determination of hazard is considered together […] Both positive and negative results shall be assembled together in a single weight of evidence determination*".

Some of the important principles relating to a weight of evidence assessment in the CLP Regulation are quoted above. A weight of evidence assessment means that data is given different weight depending on factors such as the quality and consistency of the results. Also, in relation to the statement in the CLP Regulation that "*both positive and negative results shall be assembled together in a single weight of evidence determination*" (emphasis added), this is not a matter of a majority of studies supporting one or the other outcome.

Thus, RAC is obliged to make an overall weight of evidence analysis of the complete data set. In the case of glyphosate, some studies were found to be of no weight, and were not included in the analysis, for example two studies in mice which were negative for carcinogenicity were considered to be conducted with too low doses and "*did not comply with current standards*" (CA 5.5/022, 1988 and Report no. 80 10; CA 5.5/024, 1982 original report, revised 1992) and, therefore, were considered as unacceptable.

In addition to multiple animal studies, data from the epidemiology studies and genotoxicity studies were also considered in the weight of evidence assessment. RAC concluded that despite some indications of carcinogenicity seen in some studies mainly in mice, the criteria for classification are not met when all the studies and findings are considered together. Thus, RAC reached the conclusion that no classification for carcinogenicity is warranted.

The HEAL report also refers to RAC opinions on other substances, arguing that the conclusion for no classification for glyphosate is not consistent with the classification of

these substances for carcinogenicity. However, this ignores the fact that the overall database of information in these cases is different (types of tumours and their incidences and other relevant and related data) and glyphosate has a uniquely large database on which the conclusion is made. The claim that the conclusion of RAC is not consistent with (some) other opinions is rejected.

Conclusion

France, Hungary, The Netherlands and Sweden came to its conclusion in the CLH dossier following an independent assessment of the data by the many Member State experts involved, and subsequently these data and conclusions were analysed by the independent experts of RAC. In accordance with their mandate, RAC experts applied the CLP criteria to toxicological and epidemiological findings, weighed all the evidence in arriving at their conclusions on classification of glyphosate, including for no classification for carcinogenicity. RAC's detailed assessment is provided in its adopted opinion.